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Iron deficiency anemia and anemia of chronic disease in geriatric hospitalized patients: How frequent are comorbidities as an additional explanation for the anemia?

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Aim: Anemia is an important clinical problem in older patients. The aim of the present study was to investigate whether comorbidities as an additional explanation for the severity of the anemia are frequent, and might help to explain the anemia severity in older patients with iron deficiency anemia (IDA) and the anemia of chronic disease (ACD).

Methods: In the present prospective study, 191 consecutive hospitalized older patients with IDA and the ACD were investigated. A peripheral blood count, C-reactive protein, standard iron parameters, serum vitamin B_{12} and folate, and renal and thyroidal function tests were analyzed. The attending geriatrician was responsible for the medical diagnosis and follow up.

Results: A total of 56 patients with IDA and 135 with the ACD were investigated. Just 24 patients with IDA had normal serum folate, vitamin B_{12} and thyroid-stimulating hormone levels without laboratory evidence of inflammation or chronic renal failure, but one of these patients was diagnosed with hemolytic anemia. Hence, 23 patients (41%) were diagnosed with "IDA only". "ACD only" was diagnosed in 104 patients (77%), and 22 patients (16%) with ACD had chronic renal failure. A myelodysplastic syndrome was found in two patients.

Conclusions: Additional etiologies are often diagnosed in anemic older patients, but it remains unknown to what extent these diseases might influence the pathogenesis of the anemia. Individual and clinical judgment remain crucial to evaluating and treating older anemic patients. **Geriatr Gerontol Int 2014; ••: ••–••.**

Keywords: anemia, elderly, inflammation, iron deficiency, multifactorial etiology.

Introduction

Anemia is an important clinical problem in elderly patients, and might contribute to an increased rate of morbidity and mortality. The anemia of chronic disease (ACD), also called anemia of inflammation, and iron deficiency anemia (IDA) are the two most prevalent causes of anemia in hospitalized older patients.[1,2] ACD develops in patients with an acute or chronic infection, autoimmune disease or malignancy. IDA most commonly results from chronic gastrointestinal blood loss. There are no standard diagnostic criteria to classify IDA and ACD, and their diagnosis is often a clinical challenge. Serum ferritin is the most commonly used laboratory parameter to differentiate between IDA and ACD, but it is also an acute phase reactant and its level increases with age. The usefulness of additional analyses, such as reticulocyte hemoglobin equivalent, serum hepcidin, serum transferrin receptor and serum transferrin receptor/log serum ferritin, is unclear and some of these tests are not routinely available.[3–5] In specific organ-related diseases, at least two causes contributing to the anemia were found in 63.8% anemic patients with chronic heart failure,[6] more than 50% in patients with diabetes,[7] and 63% of the anemic patients with an inflammatory bowel disease had both ACD and IDA.[8] However, it is more difficult to assess the impact of two classical hematological diseases on the hemoglobin level in the same anemic patient. Recent studies have shown that the underlying cause of the anemia is multifactorial in a substantial number of community-dwelling, as well

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Table 1 Characteristics of 56 patients with iron deficiency anemia and 135 patients with anemia of chronic disease

	IDA (n = 56)	ACD (n = 135)	P
Age (years)	84.2 (5.7)	84.3 (5.4)	0.91
Female, n (%)	34 (61)	73 (54)	0.4
Hemoglobin (g/dL)	9.5 (1.8)	10.6 (1.3)	<0.001
MCV (fL)	81 (9.5)	90.5 (6.7)	<0.001
CRP (mg/L)	13.3 (16)	96.5 (88)	<0.001
Serum iron (μg/dL)	27.4 (15.5)	27.8 (13.6)	0.69
Serum transferring (g/L)	3.2 (0.57)	1.9 (0.42)	<0.001
Saturation index (%)	6.4 (4.0)	10.5 (4.5)	<0.001
Ferritin (μg/L)	22.1 (13)	316 (256)	<0.001
Serum vitamin B_{12} (ng/L)	487 (312)	597 (359)	0.02
Serum folate (μg/L)	11.4 (5)	11.3 (4.9)	0.87
TSH (mIU/L)	1.66 (1.6)	1.42 (1.1)	0.39
eGFR (mL/min/1.73 m^2)	55.8 (18)	54.2 (23)	0.57

Values are presented as mean (standard deviation) except as otherwise indicated. ACD, anemia of chronic disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IDA, iron deficiency anemia; MCV, mean corpuscular volume; TSH, thyroid-stimulating hormone.

as in hospitalized, older anemic patients, but more detailed research is lacking.[2,9,10] Aim of the present study was to investigate the prevalence, and whether additional diseases might influence the hemoglobin level in older hospitalized patients with IDA and ACD using generally accepted laboratory and clinical criteria.

Methods

In a prospective study, we investigated 191 consecutive older patients aged 70 years and older with a diagnosis of IDA and ACD according to specific diagnostic criteria and admitted to the acute geriatric ward of a tertiary care hospital. Some of these patients participated in a previously published study on the significance of the reticulocyte hemoglobin equivalent for the diagnosis of IDA.[5] A complete blood count including mean corpuscular volume, serum ferritin, vitamin B_{12}, folate, iron, transferrin, transferrin saturation, C-reactive protein (CRP), thyroid-stimulating hormone (TSH), creatinine and the estimated glomerular filtration rate (eGFR) were analyzed according to routine laboratory methods.[5] Anemia was defined as a serum hemoglobin <13 g/dL for men and <12 g/dL for women. In our laboratory, the upper limit of normality for serum CRP is 5 mg/L and a level >5 mg/L was therefore chosen as a marker for inflammation. IDA was defined as a serum ferritin level <50 μg/L and a transferrin saturation ≤20%, irrespective of the serum CRP level.[11,12] ACD was considered present if the patient had all of the following criteria: a serum ferritin level ≥50 μg/L, serum CRP level >5 mg/L, a transferrin saturation ≤20% and the presence of a clinical diagnosis of an acute or chronic infection, autoimmune disease or malignancy.[5,11,13] Vitamin B_{12} deficiency was diagnosed if the serum vitamin B_{12} concentration was less than 200 ng/L, and folate deficiency if the serum folate level was less than 4 μg/L. An abnormal TSH level was defined if the serum level was less than 0.1 or higher than 10 mIU/L, respectively.[11] Patients with an eGFR ≤30 mL/min/1.73 m^2 were classified as having the anemia of chronic kidney disease (CKD). All patients were examined by their treating geriatrician, who was responsible for the medical follow up, technical investigations and the interpretation of the medical data. Patients treated with red blood cell transfusion or taking iron during the past 2 months were excluded. The present study protocol was approved by the ethical committee of University Hospitals Leuven, Leuven, Belgium, and patients were included after oral consent.

Statistical analyses were carried out with SPSS Statistics version 20. The Kolmogorov–Smirnoff test was used to investigate the normal distribution of the parameters. Comparison between two groups was carried out by the Student's t-test or the Mann–Whitney U-test, depending on the parametric or non-parametric distribution of the data.

Results

The clinical and laboratory characteristics of the total study population are shown in Table 1.

Table 2 comorbidities in patients with iron deficiency anemia and anemia of chronic disease

Comorbidities	*n*	*n* with CRP ≤ 5 mg/L
IDA (*n* = 56)		
IDA only	23	23
IDA and hemolytic anemia	1	1
IDA and vitamin B_{12} deficiency	1	1
IDA and CKD	3	1
IDA and thyroid dysfunction	3	0
IDA and CKD and thyroid dysfunction	1	0
IDA and myelodysplastic syndrome	1	0
IDA and other comorbidities	23	0
ACD (*n* = 135)		
ACD only	104	0
ACD and myelodysplastic syndrome	1	0
ACD and CKD	21	0
ACD and thyroid dysfunction	8	0
ACD and CKD and thyroid dysfunction	1	0

ACD, anemia of chronic disease; CRP, C-reactive protein; CKD, chronic kidney disease; IDA, iron deficiency anemia.

IDA

IDA was diagnosed in 56 patients (34 women). Just 24 of these patients fulfilled all of the following criteria: a CRP ≤ 5 mg/L, eGFR >30 mL/min/1.73 m^2, and normal serum vitamin B_{12}, folate and TSH levels. One of these patients was diagnosed with a hemolytic anemia as a result of a mechanical aortic valve repair, hence 23 patients (41%) were diagnosed as having "IDA only" (Table 2). There was also one patient each with a CRP ≤ 5 mg/L and vitamin B_{12} deficiency or CKD. A total of 30 patients had a CRP > 5 mg/L, of whom two were diagnosed with CKD, three with thyroid dysfunction, one patient with CKD and thyroid dysfunction, one patient with a myelodysplastic syndrome (MDS) and 23 without any of the aforementioned comorbidities (Table 2). It is noteworthy that in the latter 23 patients, the diagnosis of a colorectal cancer and an acute infectious condition, commonly found in patients with ACD, was made in three and 11 patients, respectively. The mean hemoglobin level in the 23 patients with "IDA only" was 8.9 ± 1.9 g/dL, as compared with 9.8 ± 1.6 g/dL in the 33 other IDA patients ($P = 0.06$). A total of 31 of the IDA patients had a serum ferritin level <20 μg/L, of whom 14 had a CRP level >5 mg/L.

The results of the upper and lower gastrointestinal endoscopic investigation in the total group of IDA patients were as follows: a benign gastrointestinal lesion (erosions and ulcers of the upper gastrointestinal tract, arteriovenous malformation, hemorrhoids) was found in 18 patients, a colorectal cancer in seven and one or more dysplastic colorectal polyps in another three patients. No cause for the blood loss was found in the other 28 patients (50%). Of the latter patients, 11 refused an esophagogastroduodenoscopy and a colonoscopy or were in a poor clinical condition, the result of an esophagogastroduodenoscopy and colonoscopy was negative in 11, and six other patients underwent an esophagogastroduodenoscopy without a specific lesion, but no colonoscopy.

ACD

ACD was diagnosed in 135 patients (73 women). All patients had a serum CRP level >5 mg/L, of whom 127 (94%) had a CRP level >10 mg/L. A total of 21 patients (16%) had an eGFR ≤ 30 mL/min/1.73 m^2, a TSH level <0.1 mIU/L or >10 mIU/L was found in eight patients (6.6%), and one patient had CKD and thyroid dysfunction (Table 2). A total of 105 ACD patients (78%) had both an eGFR >30 mL/min/1.73 m^2 and a TSH level >0.l and <10 mIU/L. One of these patients was diagnosed with a MDS during hospitalization, hence 104 patients were classified as "ACD only" (Table 2). The mean hemoglobin level in the latter 104 patients was 10.6 ± 1.4 g/dL and 10.6 ± 1.2 g/dL in the other 31 patients ($P = 0.6$). All ACD patients had normal serum vitamin B_{12} and folate levels. The prevalences of the main clinical diagnosis of an acute or chronic infection, autoimmune disease or malignancy as part of the diagnostic criteria for ACD were as follows: an acute infectious process, mainly of the respiratory tract (*n* = 50), urinary tract (*n* = 22) and gastrointestinal tract (*n* = 13) was found in 96 patients (71%); cancer in 17 patients (12.3%; prostate cancer 6, colon carcinoma 3, lung carcinoma 2, other cancers 6) and a chronic infectious process or autoimmune inflammatory disease (mainly gout, rheumatoid arthritis, giant cell arteritis/polymyalgia, chronic pressure ulcer, spondylodiscitis) was detected in 22 patients (16%).

Discussion

In the present study, we investigated to what extent additional diseases associated with anemia are of clinical significance in patients with IDA and ACD. Less than half of the patients with IDA had "IDA only," defined as a serum ferritin <50 μg/L without inflammation, chronic kidney failure, vitamin B_{12} or folate deficiency, thyroid dysfunction, or any other known cause for the anemia. The mean hemoglobin level was not statistically different between patients with "IDA only" and IDA

with additional conditions, as well as in patients with "ACD only" and ACD with additional conditions. Only one patient with vitamin B_{12} deficiency and no cases with folate deficiency were found. Besides the clinical diagnosis of an inflammatory disease, which was obligatory for the diagnosis of ACD, 16.2% and 6.7% of the ACD patients had chronic renal failure and thyroid dysfunction, respectively. In 77% of the patients with ACD, no CKD, vitamin B_{12} or folate deficiency, thyroid dysfunction, or any other additional explanation for the anemia could be diagnosed. Hence, these patients were diagnosed as "ACD only." In most studies, a single and predominant cause for the anemia is identified. This is based on clinical arguments or a predefined sequential approach in order to give priority to treatable conditions.[9,11,14] From a clinical point of view, this means that what are commonly called "nutritional anemia" (iron, vitamin B_{12} and folate deficiency) and anemia of chronic disease are mostly at the top of the list.[9,11] As a consequence, the diagnosis of anemia as a result of other etiologies, such as CKD, thyroid dysfunction or attributed to specific hematological diseases (e.g. MDS, hemolytic anemia, multiple myeloma etc.) are mostly dictated on specific clinical and laboratory grounds, or diagnosed after exclusion of other diseases.[11]

Only a few studies have focused in general on the multifactorial etiology of anemia.[2,9–11,15] In a large population of ambulatory older subjects, 5.4% of the subjects had a combination of vitamin B_{12}, folate or iron deficiency, and an additional 4.3% had renal insufficiency and ACD.[9] In a cohort of 696 ambulatory and hospitalized patients, 43% had at least two causes of anemia.[15] Petrosyan *et al*. diagnosed anemia as multifactorial in 46.3% of a cohort of 95 hospitalized older patients.[2] In the present study, the anemia was multifactorial in 33 of the 56 patients with IDA and in 31 of the 135 patients with ACD. It is rather a "semantic" discussion whether the anemia in patients with a low serum ferritin level in combination with an increased CRP level should be labeled as pure IDA, ACD or a combination of the two. Some physicians will investigate these patients for chronic gastrointestinal blood loss and will start iron supplementation. Another option could be to start a gastrointestinal exploration once the underlying inflammatory disease has been resolved, but this delay could lead to an important loss of time, especially in the case of specific gastrointestinal lesions, such as a colonic tumor or gastric ulcer. However, it is possible that this multifactorial origin of the anemia, for example, in patients with IDA, could be the trigger for the non-responsiveness to iron supplements, at least in some of these patients. In virtually all studies, the main subject of investigation in patients with IDA is the gastrointestinal tract in order to find a cause for the chronic blood loss. A potential gastrointestinal lesion as a source of the bleeding was found in 50% of our patients, and this is in accordance with other studies.[16,17] A similar "semantic" problem occurs in patients with ACD in combination with, for example, CKD. High levels of inflammatory markers, the presence of an inflammatory clinical condition in many cases, inappropriately low serum erythropoietin levels relative to the degree of anemia, and elevated hepcidin levels overlap between ACD and the anemia of CKD.[4,18–20] It is still a matter of debate whether CKD should be considered as a separate cause or as part of the ACD spectrum.[11,13,16,19–21] In the present study, more patients were diagnosed with ACD than IDA. This is in agreement with the results of Guralnik *et al*.[9] and Petrosyan *et al*.,[2] who used only laboratory criteria to define ACD. In other studies, ACD was diagnosed after the elimination of other causes or in the setting of a clinically active inflammatory disease without laboratory criteria, and a much lower prevalence for ACD as compared with IDA was shown.[11,14] A possible explanation for these disparities might be the differences in methodologies used to define the different causes of anemia and this might explain, at least partly, the wide variation of the prevalence of unexplained anemia in different studies.[2,9,11,14]

The present study had several limitations. We studied only patients with IDA and ACD according to specific diagnostic criteria, and the majority of the latter group had an acute infection. Our study was a clinical and not a physiopathological study, hence we could no show to what extent the different diseases are responsible for the anemia in each patient. The lack of generally accepted and well standardized criteria for IDA and ACD results in varying prevalences of these types of anemia in different studies, and the high prevalence of concomitant diseases complicates the interpretation of the traditional laboratory analyses. Unfortunately, serum methylmalonic acid and homocysteine analysis neither a therapeutical trial with vitamin B_{12}, folate, iron or a corrective treatment for the thyroid disease were carried out to exclude or confirm the specific diagnosis of vitamin B_{12}, folate and iron deficiency or a thyroid dysfunction, but patients were treated on an individual basis by their attending geriatrician. We studied a group of older hospitalized patients with a geriatric profile (multimorbidity, atypical presentation of clinical symptoms, polypharmacy, frailty, cognitive impairment etc.). Hence, the present results cannot be generalized to other ambulatory or hospitalized elderly patients. A bone marrow investigation is often deferred or refused by patients, and was only carried out as proposed by the responsible geriatrician. A bone marrow aspirate is not always diagnostic for iron deficiency.[22] However, it is useful in patients with unexplained anemia and suspicious laboratory abnormalities, such as unexplained macrocytosis, neutropenia, thrombocytopenia or pancytopenia, in order to diagnose specific hematological diseases, such as MDS or other hematological

malignancies. MDS was diagnosed in two patients, and this is probably an underestimation as compared with our previously published report.[1] However, anemia was already attributed to IDA or ACD, and MDS remains a relatively rare disease, even in elderly patients.[1,11] Other laboratory parameters, such as the serum transferrin receptor analysis or hepcidin, are valuable tests for the evaluation of the iron status and the differential diagnosis between IDA and ACD, but these tests are not routinely available or not well standardized.[3,4,12,23]

In conclusion, the diagnosis of IDA and ACD is not straightforward in older patients. Additional diseases that could modify the hemoglobin levels are often diagnosed in these patients. An inflammatory disease is a frequent comorbidity in patients with IDA, as is chronic renal failure in patients with ACD, but the presence of comorbidities did not influence the severity of the anemia. Individual and clinical judgment favoring the predominant and potentially treatable cause for the anemia remain crucial to evaluating and treating older anemic patients until more accurate criteria become available. Further research is required to determine which diagnostic and therapeutic options are optimal for patients with a multifactorial anemia.

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